REMARKS

This is in response to the Office Action that was mailed on November 16, 2006. Claim 2 is cancelled, without prejudice. Claim 1 is amended to recite only cyclosporin A as a cyclophilin ligand and to specify that the inventive method contemplates use thereof only when the cyclosporin A is able to cross the blood brain barrier. New claim 18 is added, directed to a specific technique of crossing the blood brain barrier, as disclosed in Example 1. No new matter is entered by this Amendment. Claims 1 and 3-18 are pending in the application.

Objection was raised to claim 2. Claim 2 has been cancelled, obviating the objection stated by the Examiner.

Claims 1-17 were rejected under the first paragraph of 35 U.S.C. § 112, as exceeding the scope of the enablement. The Examiner kindly indicated that the species cyclosporin A was enabled, at least insofar as the claim definition of the active agent in the present invention. The Examiner also addressed the issue of the necessity for purposeful disruption of the blood brain barrier. This feature of the invention was addressed by Applicants in the specification. See e.g. paragraph [0026] therein, which indicates that administration of the treatment medication (i.e., cyclosporin A) via any means with purposeful disruption of brain or spinal parenchyma, or disrupting the blood-brain barrier via mechanical, thermal, cryogenic, chemical, toxic, receptor inhibitor or augmentor, p-glycoprotein transporter poisoning, inhibition or saturation, osmotic, charge altering, radiation, photon, electrical or other energy or process is included in the invention. The language of claim 1 has been adjusted to more clearly reflect this aspect of the present invention. Step (a) in claim 1 now reads "(a) preparing a dosage of cyclophilin ligand for parenteral or enteral administration, said cyclophilin ligand being cyclosporin A, when able to cross the blood-brain barrier, said dosage being from 0.001 to 50 mg/kg of body weight of said mammal for parenteral administration and from 0.01 to 60 mg/kg of body weight of said mammal for enteral administration". As a general comment, it is not believed to be necessary to list the ways of getting cyclosporin A across the BBB, since those ways are well know to persons

skilled in the relevant art. For example, lumbar puncture injection, Ommaya reservoir, and intracerebroventricular infusion are commonly employed approaches, to name just a few. The Examiner notes that "no actual results are provided" in the specification. As the Examiner will appreciate, the function of the specification is to teach persons skilled in the relevant art how to practice the invention. There is no requirement to report actual clinical results obtained by using the invention in the specification. It is respectfully submitted that – with respect to the claims currently pending herein – Applicants' specification fully enables their invention.

Claims 1-5 and 9-14 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 96/22104 to Eskil Elmer, Marcus Keep, *et al.* (Elmer). Office Action, pages 5-6. The rejection is respectfully traversed.

The present invention is quite different from, and not anticipated by, the Elmer reference. The present invention involves the novel and unobvious concept that the treatment of primary and metastatic brain tumors and other brain lesions can be improved by the action of cyclosporin. In this invention, the cyclosporin acts preferentially to protect neurons from radiation, while not "protecting" brain tumor cells from the same radiation. This important method is not foreshadowed in Applicants' earlier Elmer disclosure.

Elmer's teaching of cyclosporin as a neuroprotectant is silent as to whether cyclosporin is protectant, neutral, or harmful to other types of tissues subject to radiation insult, such as tumor cells. Elmer does not once mention cyclophilin or any ligand to which cyclosporin might bind. Accordingly, it cannot be said that the Elmer disclosure anticipates the present invention.

Elmer discloses that cyclosporins are neuroprotective by the mechanism of protecting the intracellular biochemistry, form, function, and organelles from irreversible damage during the loss of cellular homeostasis. The pathway from cell damage to cell death is blocked by this neuroprotective agent, so that once the physiologic disruption passes, the cell is able to reestablish equilibrium and repair the damage instead of dying. Elmer is silent as to the effects of cyclosporin beyond nervous tissue. There is no indication in the Elmer disclosure that cyclosporin is not as powerful a protectant of tumor cells as it is of neurons.

Withdrawal of the rejection of claims 1-5 and 9-14 as being anticipated by WO 96/22104 is in order and is respectfully solicited.

Claims 6-8 and 15-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/22104 to Eskil Elmer, Marcus Keep, *et al.* (Elmer) in view of *Advances in Neurology* 56:341-353 (Bradley) and *Comments Toxicol.* 2:253-263 (Pellmar). The rejection is respectfully traversed.

The Examiner characterizes the differences between Applicants' invention and the prior art as being minor. Applicants respectfully contend that their invention, whether or not "minor", when considered as a whole is not obvious from the various pieces of prior art assembled by the Examiner in this rejection. Even minor or incremental inventions are worthy of patent protection, because they provide the public with previously undiscovered technology.

Focusing for a moment on claims 6, 7, 15, and 16, it is noted that the Examiner has conceded that the prior art does not teach treatment of cancer patients. How then does the Examiner justify rejecting, for instance, claim 15 ("A method for selectively reducing neuron death from ionizing radiation in cyclophilin-rich neurons of central, peripheral, and autonomic nervous systems of a cancer patient with a primary brain tumor while not reducing damage or death to cyclophilin-poor cells and tissues selected from the group consisting of glia, glia-derived tumor cells, abnormal neuron-derived tumor cells, non-brain tumors, and non-neuron tissue of the body, said method comprising the steps of: (a) preparing a dosage of cyclosporin A, said dosage being from an effective amount to less than 1 gr/kg of body weight of said cancer patient; and (b) administering said dosage to said cancer patient before, co-incident with, or after ionizing radiation of said cancer patient, said dose being administered not later than the same day as the radiation exposure")?

Applicants respectfully disagree with the Examiner that the average practitioner of the art would be motivated by Elmer, Pellmar, and Bradley to treat brain cancer patients with cyclosporin and radiation. The average practitioner of the art would be a radiation oncologist, who administers radiation to cancer patients, and would be ignorant as to the neuroprotective effects of cyclosporin. The average radiation oncologist, even if presented with the teachings of

Elmer, Pellmar, and Bradley together, would see no evidence providing motivation to administer cyclosporin to brain tumor patients receiving radiotherapy. As the Examiner recognizes, cyclosporin might be effective against "cell death" in general from radiation. The Elmer description that cyclosporin protects a cell's biochemical machinery and organelles would raise the real concern that cyclosporin could be just as radioprotective to tumor cells as to neurons. This would actually discourage the use of cyclosporin as having no net benefit, while exposing the patient to the known toxicities of cyclosporin, including immunosuppression and nephrotoxicity. The perceived lack of net benefit and the real toxicities of cyclosporin would remove any motivation of the practitioner to administer cyclosporin concomitant with radiotherapy to treat brain tumors.

Withdrawal of the rejection of claims 6-8 and 15-17 as being unpatentable over WO 96/22104 in view of Pellmar and Bradley is in order and is respectfully solicited.

It is respectfully submitted that none of claims 1 and 3-18 is anticipated by or obvious from Applicants' prior work as embodied in WO 96/22104, alone or in combination with Pellmar and Bradley.

If the Examiner has any questions concerning this application, he is invited to contact Richard Gallagher, Registration No. 28,781, at (703) 205-8008.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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